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The necessity of identifying the basal glucose set-point in the IVGTT for patients with Type 2 Diabetes

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Abstract

Background: The model-based dynamic insulin sensitivity and secretion test (DISST) uses fasting glucose (G_0) as the basal glucose (G_B) concentration when assessing insulin sensitivity (S_I). However, this model was developed in a healthy, normoglycaemic cohort. We sought to determine the suitability the DISST model has for individuals with established type 2 diabetes (T2D).

Methods: 14 participants with established T2D were recruited to take part in a dietary intervention study. Insulin-modified intravenous glucose tolerance tests (IM-IVGTT) were undertaken at week 0, 12 and 24 and were used with DISST model to identify G_B . A total of 36 tests were conducted across 12 participants throughout the study. Measured G_0 and identified G_B values were compared using a Kolmogorov-Smirnov (KS) and signed rank (RS) test for the cohort.

Results: There were significant differences between the G_0 and identified G_B values in this cohort (p_{rs} and $p_{ks} < 0.0001$), although both values were well correlated ($R = 0.70$). The residual plot demonstrates that the modified model captures the behaviour of the participants more accurately than the original model.

Conclusions: This analysis has shown that G_B is an important variable for modelling the glycaemic behaviour in T2D. These findings suggest that the original DISST model, while appropriate for normoglycaemic cohorts, needs to model basal glucose level as a variable for assessing individuals with established T2D.

Keywords: Basal glucose concentration, DISST, Insulin resistance, Insulin sensitivity

Background

Type 2 diabetes mellitus (T2DM) is a metabolic disease that affects the body's ability to regulate glucose concentrations [1-3]. T2DM is characterized by fasting and post-prandial hyperglycaemia [4] and causes comorbidities with significant personal and economic cost [5]. The hyperglycaemia is attributed to a combination of impaired insulin utilization (insulin resistance) and a limited ability to compensate with insulin production (net insulin deficiency).

The ability to quantify both insulin sensitivity and insulin secretion is essential to improving the understanding of the complex physiology underlying type 2 diabetes. Mathematical models of glycaemic dynamics have been coupled with clinical data to identify key aspects in the pathogenesis of type 2 diabetes. The dynamic insulin

sensitivity and secretion test (DISST) incorporates a clinical protocol similar to the insulin-modified intravenous glucose tolerance test (IM-IVGTT) [6,7] and measures the participant glucose, insulin and C-peptide responses. The DISST data modelling and data fitting methods were customized to the clinical protocol and allow a robust measurement of insulin sensitivity (SI) that avoids the problems encountered with IVGTT assessment in insulin resistant patients [8-11]. The DISST SI value is highly correlated to the euglycaemic hyperinsulinaemic clamp (EIC) SI value ($R = 0.81$), which is widely regarded as the reference method [12].

However, the DISST model uses the participant's measured fasting glucose concentration (G_0) as their basal glucose concentration (G_B). The G_B term in the DISST model effectively has the role of determining the set-point towards which the modelled glucose response tends, where this choice matches assumptions in all other model-based tests [6,9,13-15]. However, the DISST model was developed in a relatively healthy, normoglycemic cohort [16,17]. In contrast, studies show that G_0 levels and insulin concentrations are slightly higher in the morning than their overnight "basal" levels, especially for participants with diabetes [18-21]. Therefore, the evidence suggests that G_B and G_0 should be treated as separate entities for individuals with established diabetes as the levels are determined by relative insufficiencies in SI , endogenous insulin secretion (U_N) and rates of gluconeogenesis [22-24].

We sought to determine whether a novel modelling approach that identifies G_B as a variable in individuals with established type 2 diabetes more accurately reflects glucose dynamics.

Methods

Participants

Fourteen individuals with established type 2 diabetes mellitus were recruited from the Wellington region of New Zealand to take part in an Atkins-Based low carbohydrate dietary intervention study. Recruited participants were aged between 30 and 65 with a BMI range of 34 to 46 $\text{kg} \cdot \text{m}^{-2}$ at baseline. Participants were excluded if they had major physiological or psychological illness at the time of testing. Pregnant or lactating females were also excluded. Two participants discontinued the intervention, the first citing personal reasons, and the second left the study due to a renal stone. Twelve participants each underwent three IM-IVGTT over a 24 week period resulted in a total of 36 tests for the study. Participants had their age and BMI recorded (median [IQR]; 47.5 [42.5, 54.5] and 40.40 [37.48, 43.48], respectively). Full demographic details and results of the intervention study have been previously described [25]. Ethics approval for this study was provided by the New Zealand Ministry of Health, Central Regional Ethics Committee.

Clinical procedure

The clinical protocol utilised in this study was similar to the protocol defined by Ward *et al.* [7]. A $0.2 \text{ g} \cdot \text{kg}^{-1}$ glucose bolus was administered at $t = 1$ minute and then an infusion of insulin that was intended to replicate the insulinaemic response of a normoglycaemic individual was administered. An insulin infusion was started at $t = 2$ minutes at a rate of $3.5 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and was reduced to $0.5 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at $t = 7$ minutes. Further reductions occurred at $t = 17$ minutes, to $0.25 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and at $t = 50$ minutes, to $0.1 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The infusion of $\text{mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was maintained for the

remainder of the procedure. Venous blood samples were taken into fluoride oxalate tubes at times: $t = -10, -5, -1, 0, 2, 3, 4, 5, 6, 8, 10, 12.5, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 210, 240, 270$ and 300 minutes. Blood samples were assayed for glucose and insulin concentration using standard commercial assays at an accredited laboratory.

Model

Dynamic Insulin Sensitivity and Secretion Test (DISST) Model

This analysis used the DISST models of interstitial insulin kinetics and glucose dynamics [16,17]:

$$\dot{Q} = \frac{n_I}{V_Q} I - \left(n_C + \frac{n_I}{V_Q} \right) Q \quad (1)$$

$$\dot{G} = -p_G(G - G_B) - SI(GQ - G_B Q_B) + \frac{P_X}{V_G} \quad (2)$$

where equation nomenclature is shown in Table 1.

V_Q , n_I and n_C are defined a-priori based on anatomical functions [17,26-28] while DISST model sets p_G as a constant at 0.004 min^{-1} [17].

Parameter identification

Interstitial insulin (Q) was simulated via integrating factors and a linear interpolation of I .

$$Q = e^{-\int_0^t n_C + \frac{n_I}{V_Q} dt} \left(Q_0 + \int_0^t e^{\int_0^t n_C + \frac{n_I}{V_Q} dt} \frac{n_I}{V_Q} I dt \right) \quad (1a)$$

where Q_0 is determined assuming a steady state at $t = -10$ minutes:

$$Q_0 = \frac{\frac{n_I}{V_Q} I_0}{n_C + \frac{n_I}{V_Q}} \quad (3)$$

Table 1 Nomenclature of the DISST model

Variable	Unit	Description	Role
I	$\text{mU} \cdot \text{L}^{-1}$	Plasma insulin concentration	Measured
G	$\text{mmol} \cdot \text{L}^{-1}$	Plasma glucose concentration	Measured
G_B	$\text{mmol} \cdot \text{L}^{-1}$	Basal plasma glucose concentration	Measured
Q	$\text{mU} \cdot \text{L}^{-1}$	Interstitial insulin concentration	Simulated
Q_B	$\text{mU} \cdot \text{L}^{-1}$	Basal interstitial insulin concentration	Simulated
V_Q	L	Interstitial insulin distribution volume	a-priori
n_I	$\text{L} \cdot \text{min}^{-1}$	Plasma-interstitial diffusion rate	a-priori
n_C	min^{-1}	Interstitial insulin degradation rate	a-priori
P_X	$\text{mmol} \cdot \text{min}^{-1}$	Exogenous glucose input rate	a-priori
p_G	min^{-1}	Non-insulin mediated glucose disposal rate	a-priori
V_G	L	Glucose distribution volume	Identified
SI	$\text{L} \cdot \text{mU}^{-1} \cdot \text{min}^{-1}$	Insulin sensitivity	Identified

The DISST model typically sets G_B as equal to G_0 [16,17]. Hence, G_0 acts as a surrogate basal glucose concentration level. However, for individuals with elevated fasting glucose, this assumption may not be accurate [18-21], and should be tested.

In this analysis, G_B was identified in concert with SI and V_G . The typical approach used with the DISST model identifies only SI and V_G . Thus, the outcomes of the three-parameter (G_B , SI , V_G) model were compared to the outputs of the typical two-parameter model (SI , V_G).

A Gauss Newton parameter identification method was used to identify the participant-specific models, with objective function defined:

$$\mathbf{x}_{i+1} = \mathbf{x}_i - \alpha (\mathbf{J}^T \mathbf{J})^{-1} \mathbf{J}^T \boldsymbol{\psi} \quad (4)$$

where $\mathbf{x}_i = [G_{Bi}, SI_i, V_{Gi}]^T$ and i is the iteration number. The Jacobian matrix (\mathbf{J}) and the residual matrix ($\boldsymbol{\psi}$) are defined:

$$\mathbf{J}(\mathbf{x}_i) = \begin{bmatrix} \frac{\delta \psi_1}{\delta G_{Bi}} & \frac{\delta \psi_1}{\delta SI_i} & \frac{\delta \psi_1}{\delta V_{Gi}} \\ \frac{\delta \psi_2}{\delta G_{Bi}} & \frac{\delta \psi_2}{\delta SI_i} & \frac{\delta \psi_2}{\delta V_{Gi}} \\ \vdots & \vdots & \vdots \\ \frac{\delta \psi_n}{\delta G_{Bi}} & \frac{\delta \psi_n}{\delta SI_i} & \frac{\delta \psi_n}{\delta V_{Gi}} \end{bmatrix}, \quad \boldsymbol{\psi}(\mathbf{x}_i) = \begin{bmatrix} G(\mathbf{x}_i, t_1) - G_S(t_1) \\ G(\mathbf{x}_i, t_2) - G_S(t_2) \\ \vdots \\ G(\mathbf{x}_i, t_n) - G_S(t_n) \end{bmatrix}$$

where n is the number of measured samples, $G(\mathbf{x}_i, t_i)$ is the modelled glucose concentration at $t = t_i$ given \mathbf{x}_i , $G_S(t_i)$ is the measured glucose level at $t = t_i$.

The Jacobian was numerically evaluated using perturbations of $[\delta G_B, \delta SI, \delta V_G] = [10^{-3}, 10^8, 10^{-3}]$. These perturbation values were 0.1% of the order of magnitude of the expected parameter values. Glucose samples between $t = 1$ and $t = 10$ minutes were disregarded by the identification methods, as this period is heavily influenced by mixing kinetics that are not captured by the whole body model of glucose metabolism [17,29].

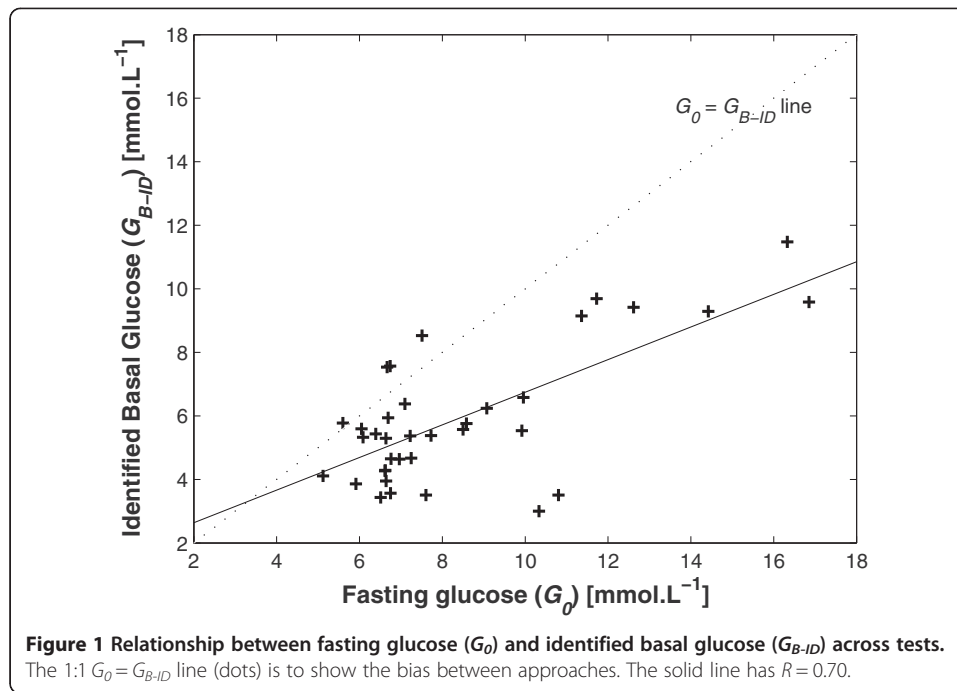
Identifying G_B in concert with SI and V_G can cause identified parameter trade off in some cases [8]. The value of V_G was thus limited to physiologically measured bounds from other studies [16,17,30,31]. In particular, V_G was limited to the range of $[0.12Bw, 0.25Bw]$ where bodyweight (Bw) is measured in kg and the coefficients have units of $\text{L} \cdot \text{kg}^{-1}$, which is a standard estimation approach linking volume to an easily measured value. Similarly, G_B was limited to a minimum of $3 \text{ mmol} \cdot \text{L}^{-1}$.

Analysis

Model residuals and interpretation of population trends were used to assess the performance of the G_B identified - DISST model. The p -values are defined with signed ranksum (p_{rs}) and Kolmogorov Smirnov test (p_{ks}) to assess median and variability. All analysis was undertaken using MATLAB (R2013b, Mathworks, Inc., Natick, MA, USA).

Results

Figures 1 and 2 shows the individual relationships between fasting glucose, (G_0), identified basal glucose (G_{B-ID}) and identified SI from normal DISST and G_B -identified DISST model across all participants and tests. Note the bias about the 1:1 line indicating that on average, the identified, model-based basal set point for glucose was significantly lower than the fasting rate for this cohort with diabetes. Figure 1 shows there



were significant differences between the G_0 and G_{B-ID} values in this cohort (Signed-ranksum: $p_{rs} < 0.0001$, Kolmogorov Smirnov: $p_{ks} < 0.0001$). In general, G_0 was higher than the G_{B-ID} value, with only 4 exceptions over 36 results (11.1%). Although there was a significant difference in the levels of G_{B-ID} and G_0 , they were relatively well correlated ($R = 0.70$), indicating moderately consistent bias in the relationship between values.

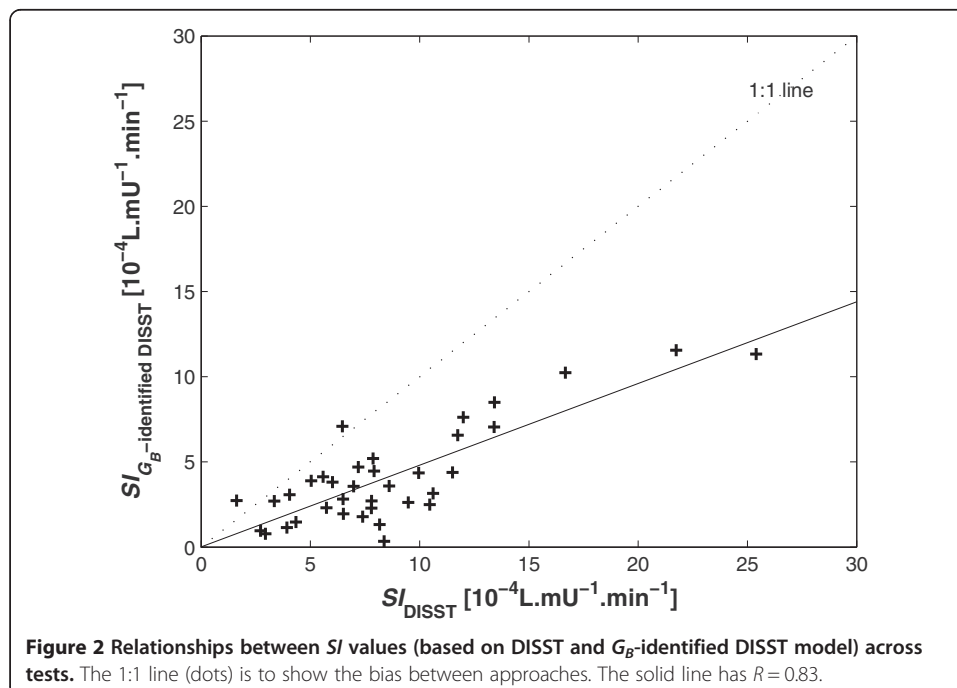
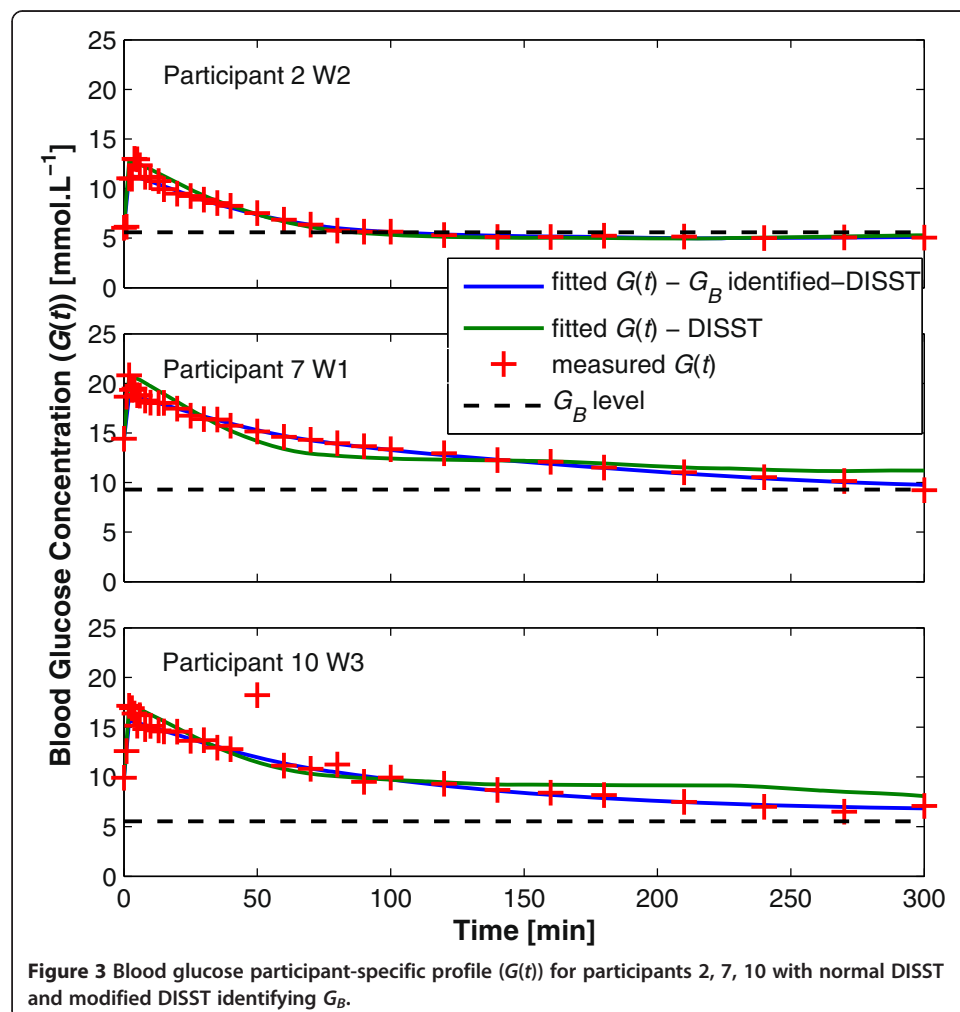


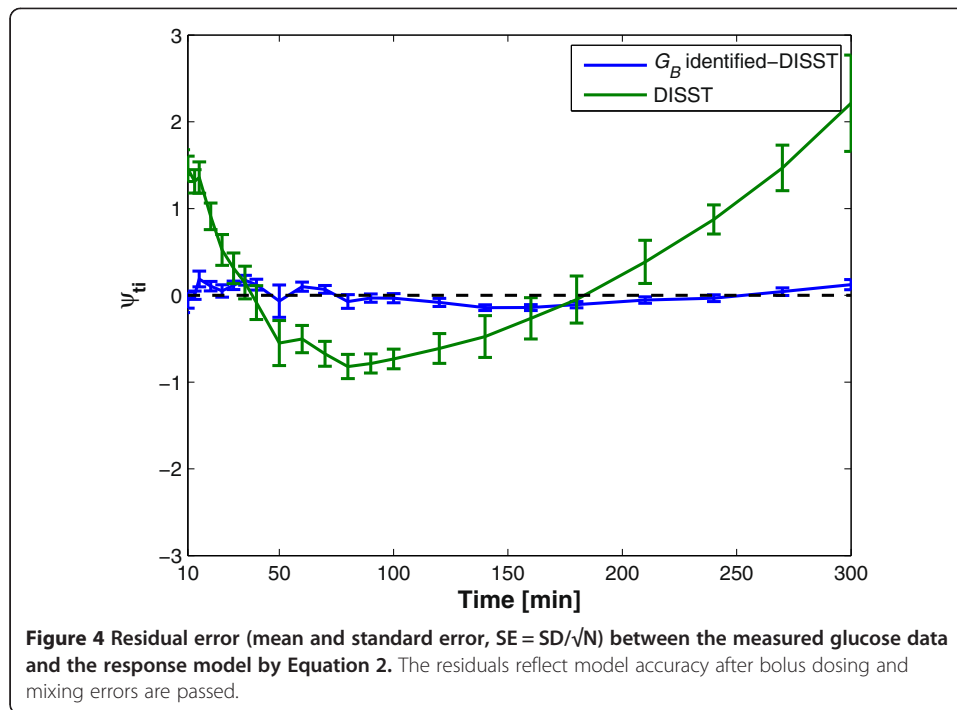
Figure 2 shows the effect that identifying G_{B-ID} has on identified insulin sensitivity values. There is a reasonably strong correlation between the SI values between normal DISST and G_B -identified DISST model ($R = 0.83$). The bias indicates that by identifying basal glucose, the model captures consistently lower SI values for those with established T2DM.

Figure 3 shows the fitted glucose profiles and measured glucose data from 3 different participants. It also shows that the identified G_{B-ID} levels are well below than G_0 as depicted in Figure 1. Figure 4 illustrates the residual errors of both the typical DISST model and the proposed three parameter identified model that identifies basal glucose. Note that the glucose samples taken within 10 minutes of glucose injection were ignored due to un-modelled mixing effects.

Discussion

This is the first study to demonstrate that glucose excursions are more accurately modelled using basal glucose as the variable in the DISST model, rather than fasting glucose for individuals with established type 2 diabetes. The typical approach employed when using the DISST model defines the fasting glucose (G_0) as the basal glucose





concentration (G_B). Hence, the glucose response defined by the original model typically tends towards the measured basal value. However, this analysis has shown that this assumption is not valid for a cohort with established diabetes. This discrepancy in the assumption is evidenced by the significant distinction in the values of G_0 and G_B that reduces as the participant glycaemic control improved across the time points of the dietary intervention study [25]. Figure 1 shows that while most participants had elevated fasting glucose levels, the identified basal level was often much closer to a lower value seen in healthy subjects. In particular, 14 of the 36 G_B values identified were in the normal reference range of $4\text{--}5.6\text{ mmol}\cdot\text{L}^{-1}$ [32] while only two of 36 G_0 values were in that range.

However, there were some participants for whom G_{B-ID} remained very high throughout the intervention. Of the three participants that exhibited G_{B-ID} values greater than $9\text{ mmol}\cdot\text{L}^{-1}$, two were first diagnosed 10 years prior to the trial. In contrast, the mean duration of diabetes for the whole cohort was 4.4 years ($SD = 1.0$ year). This outcome indicates a possible mechanism of dysfunction in type 2 diabetes that develops during the course of the disease, and matches growing dysfunction over time in these individuals. However, this study lacks the numbers required for conclusive proof of this trend.

Figure 2 shows the effects of insulin sensitivity (SI) values have from identified G_B values are significantly lower than G_0 values particularly for these type 2 diabetes participants. Hypothetically, if models to set G_B to be equal to G_0 , SI will account for low glucose level rather than G_B and is thus modelled as a higher SI value. A recent study shows that the type 2 diabetes subjects have SI values in the magnitude of $2\text{--}4 \times 10^{-4}\text{ L}\cdot\text{mU}^{-1}\cdot\text{min}^{-1}$ [16]. Although, there is not enough evidence to prove the agreeable range of SI value for type 2 diabetes participants, it is understandable that lower SI value contributes to the pathogenesis of type 2 diabetes as SI is inversely proportional to insulin resistance (IR) [3].

Figure 3 shows the blood glucose profiles of three participants as modelled by the typical two-parameter (SI , V_G) and three-parameter (G_B , SI , V_G) DISST model. While the typical two-parameter DISST model fails to fully capture the responses of the participants, the amended three-parameter model captures the behaviours more closely. This outcome is confirmed by the residual plots in Figure 4 that indicate a much smaller, yet consistent trend about the measured data. This change implies the modified model captures previously un-modelled effects or poor a-priori estimates in the interstitial insulin kinetic model.

The original DISST model was developed [17] and validated [12] in relatively normo-glucose tolerant cohorts. In these cohorts, the incidence of impaired fasting glucose was relatively low, and thus, the assumption of G_0 equals to G_B was well founded. However, the glycaemic behaviour of the cohort used in this analysis showed that this assumption was most likely to be invalid. In particular, the lower glucose levels achieved in the later part of the test would be falsely attributed to insulin sensitivity rather than a G_B value that was lower than G_0 . The significantly biased residuals showed in Figure 4 show that the typical DISST model cannot capture all dynamics of this cohort without identifying G_B directly.

Overall, these results indicate that the original two-parameter approach, while appropriate for normoglycaemic cohorts [16,17], is less suitable for individuals with established type 2 diabetes. Furthermore, it is most likely that the outcomes of this study would be applicable to pre-diabetic individuals that have elevated blood glucose. However, this assertion remains to be determined.

Neither DISST approach accurately captures the peak value of the measured blood glucose data. This particular result was due to the disregarded glucose data within 10 minutes of glucose injection. This data was rejected due to the unmodelled effects of intravascular mixing [29]. A second compartment to model local/global mixing kinetics could have been added. However, this addition was deemed unnecessary, as such compartments do not add value to the DISST modelled outcomes [17]. The approach used was intended to avoid over-fitting to mixing effects or fitting the simple DISST model of global glucose dynamics to the local glucose mixing data.

Although, this analysis was done in a small cohort, the outcomes are significant as it has shown that G_B is an important variable when modelling the glycaemic behaviour in type 2 diabetes. It also showed that G_B can be quite different to the typically assumed G_0 value, and that it may also have some diagnostic value. These findings suggest that the G_B value should be treated as a variable in DISST model for this cohort. Further validation in a much larger cohort will provide a solid foundation for these findings.

Conclusions

This analysis has shown the presence of a dysfunction in the basal (set-point) glucose in individuals with type 2 diabetes. The magnitude of the dysfunction has been shown to be linked to insulin sensitivity and the degree of fasting glucose. This analysis suggests that the basal glucose is a more appropriate variable for individuals with type 2 diabetes, as using the fasting glucose measurement as the basal set-point was shown to be a poor assumption for this cohort - although this requires confirmation in a larger study with a clamp as the reference.

Abbreviations

Physiological conditions; T2DM: Type 2 diabetes mellitus; Insulin sensitivity tests; EIC: Euglycaemic hyperinsulinaemic clamp; IVGTT: Intra-venous glucose tolerance tests; IM-IVGTT: Insulin-modified IVGTT; DISST: Dynamic insulin sensitivity and secretion test; Blood assays; G_G : Fasting glucose; G_B : Basal glucose; G_{B-ID} : Identified basal glucose; Common model parameters; S_I : Insulin sensitivity ($L \cdot mU^{-1} \cdot min^{-1}$); U_{NI} : endogenous insulin secretion ($mU \cdot min^{-1}$); I : Plasma insulin concentration ($mU \cdot L^{-1}$); G : Plasma glucose concentration ($mmol \cdot L^{-1}$); G_B : Basal plasma glucose concentration ($mmol \cdot L^{-1}$); Q : Interstitial insulin concentration ($mU \cdot L^{-1}$); Q_G : Basal interstitial insulin concentration ($mU \cdot L^{-1}$); V_G : Interstitial insulin distribution volume (L); n_I : Plasma-interstitial diffusion rate ($L \cdot min^{-1}$); n_G : Interstitial insulin degradation rate (min^{-1}); P_G : Exogenous glucose input rate ($mmol \cdot min^{-1}$); p_G : Non-insulin mediated glucose disposal rate (min^{-1}); V_G : Glucose distribution volume (L).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NAO contributed to the concept design, analysis, and drafting of the manuscript. PDD contributed to the concept design, analysis and edited the manuscript. JGC contributed to the analysis and manuscript editing. JDK and DAB contributed to the manuscript editing and data presentation. None of the authors have any conflict of interest associated with the contents of this manuscript. All authors read and approved the final manuscript.

Acknowledgements

Ministry of Higher Education, Malaysia and the University of Technology MARA, Penang, Malaysia are acknowledged for providing research funding.

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Received: 4 September 2014 Accepted: 16 February 2015

Published online: 03 March 2015

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